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FILE:

March 10, 1992

ARCD:010

Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Re: SN 07/784,222 --METHODS AND COMPOSITIONS FOR THE DETECTION OF CHROMOSOMAL ABERRATIONS-- Carol A. Westbrook

Dear Sir:

Enclosed for filing in the above-referenced patent application is an Information Disclosure Statement, PTO-Form 1449 and References.

Please stamp and return the enclosed postcard evidencing receipt of these materials.

Respectfully submitted,

David L. Parker
Reg. No. 32,165

PAR/be.01
Enclosures

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on March 10, 1992
(Date of Deposit)
David L. Parker
Name of Applicant, assignee, or Registered Representative
Signature
March 10, 1992
Date of Signature

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Carol A. Westbrook	§	
	§	Group Art Unit: Unknown
Serial No. 07/784,222	§	
	§	Examiner: Unknown
Filed: October 28, 1991	§	
	§	Atty. Dkt.: ARCD:010/PAR
For: METHODS AND COMPOSITIONS FOR THE DETECTION OF CHROMOSOMAL ABERRATIONS	§	

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on March 10, 1992 (Date of Deposit)

David L. Parker (Name of Applicant, assignee, or Registered Representative)

(Signature)

March 10, 1992 (Date of Signature)

INFORMATION DISCLOSURE STATEMENT

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

In compliance with the duty of disclosure under 37 C.F.R. § 1.56, it is respectfully requested that this Information Disclosure Statement be entered and the documents listed on attached Form PTO-1449 be considered by the Examiner and made of record. Copies of the listed documents are enclosed for the convenience of the Examiner.

In accordance with 37 C.F.R § 1.97(b), this Information Disclosure Statement is not to be construed as a representation that a search has been made or that no other possibly material information as defined in 37 C.F.R § 1.56(a) exists.

The comments contained in this Information Disclosure Statement are believed to constitute a concise explanation of the relevance of each listed document to the invention claimed in the present application. 37 C.F.R § 1.98(a). These comments,

however, are not intended to take the place of the Examiner's complete consideration of each listed reference.

R f r nc A1 (Stephenson et al., U.S. Patent 4,681,840, 1987) relates to the use of single-stranded DNA probes in the detection of oncogenes in chromosomal DNA. In particular, a 5.8 kb probe derived from human chromosome 22 is described which is said to be of use in the detection of the abnormal Philadelphia (Ph) chromosome associated with chronic myelogenous leukemia (CML). See also related application B1, discussed below.

Reference A2 (Witte et al., U.S. Patent, 4,559,305, 1986) relates to methods and compositions for the detection of CML. The method is said to be based upon the immunoprecipitation of an aberrant protein, P210, characterized as a 210kD c-abl tyrosine kinase. The antisera for use in such a method are reportedly raised by immunizing rabbits with either trpE-abl fusion proteins or v-abl peptides linked to a carrier protein.

Reference B1 (Gray et al., European Patent Application, 0,430,402, 1991) concerns methods and compositions for chromosome-specific staining using nucleic acid probes greater than 50kb in length. The methods disclosed relate to the detection of genetic rearrangements, and in particular, to the detection of the BCR-ABL fusion, for use in CML diagnosis.

Reference B2 (Groffen et al., European Patent Application, 0,181,635, 1986) relates to nucleic acid probes and methods said to be useful in the detection of chromosome translocations such as the chromosome 22 Philadelphia translocation. The identification

of hybrid *bcr*/c-*abl* mRNA transcripts by Northern blotting is described (p 45-47). The detection of the Philadelphia translocation is said to be useful in the diagnosis of CML, acute lymphocytic leukaemia and acute myelocytic leukaemia.

Reference C1 (Tkachuk et al. Science, 250:559-562, 1990), relates to the detection of *bcr-abl* fusion in CML by two color fluorescence *in situ* hybridization (FISH). Using probes from each gene, the *bcr-abl* fusion was reported detected in individual blood and bone marrow cells from 6/6 CML patients, 3 of which are said to be cytogenetically Ph^1-negative.

Reference C2 (Anastasi et al., Am. J. Pathol., 136(1):131-139, 1990) relates to the detection of numerical chromosomal abnormalities in neoplastic haematopoietic cells by *in situ* hybridization with a chromosome-specific probe. It is reported that monosomy 9 or trisomy 9 can be identified using a chromosome 9-specific biotinylated DNA probe and an avidin-based detection system. The results are said to demonstrate that interphase cytogenetic analysis is feasible in peripheral blood and bone marrow specimens and this is proposed to be of use in monitoring patients with haematopoietic malignancies.

Reference C3 (Gray et al., Bone Marrow Transplantation, 6:14-19, 1990) concerns analytical approaches to the detection and characterization of disease-linked chromosome aberrations. Flow karyotyping (FK) and fluorescence *in situ* hybridization (FISH) are said to have importance in cytogenetic analyses. The use of repeat sequence, whole chromosome composite, and locus-specific

probes in FISH techniques are outlined. FK and FISH are reportedly suited to quantitative analyses of DNA content and to the detection of aneuploidy and/or chromosome structural changes, respectively.

Reference C4 (Grossman et al., Am. J. Hum. Genet., 45:729-738, 1989) reports that the bcr exon 3 on chromosome 22 may play a role in determining the duration of CML. Following fine mapping studies, breakage is stated to be largely confined to a segment between *bcr* exons 2 and 4. Although not statistically significant, the results are said to suggest that the presence or absence of exon 3 may account for some variability in CML duration; and that the *phl/abl* protein may affect the evolution of the disease.

Reference C5 (Hutchins et al., Aust. N.Z. J. Med., 19:443-448, 1989) relates to the detection of chromosome 22 break point cluster region (bcr) rearrangement and the diagnosis of CML. 39/40 patients with CML (37/37, Ph-positive; Table 1), but 0/29 patients with other haematological disorders, are said to have rearrangements within the bcr. Two hybridization probes are reportedly necessary to detect these bcr rearrangements.

Reference C6 (Westbrook, Blood Reviews, 2:1-8, 1988) reviews the role of the abl oncogene in human leukaemias. It is said that the role of abl on the Philadelphia chromosome in Ph-positive acute lymphoblastic leukaemia is likely to be similar to that in CML, and to involve the production of a protein with aberrant tyrosine kinase activity (p 7, col 1, ¶ 2).

R ference C7 (Blennerhassett et al., Leukaemia, 2(10):648-657, 1988) presents a clinical evaluation of a DNA probe assay for the Ph^1 translocation in CML. Southern blotting with a *phl*/bcr-3 probe is said to allow the identification of CML in 190/191 Ph^1-positive cases and in 12/27 other CML patients (Table 1). The assay can reportedly detect 1% of leukaemic cells within a sample, and is proposed to be of use in the monitoring of patients (p 654, col 2, ¶ 4).

Reference C8 (Bartram et al., Blut, 55:505-511, 1987) relates to the identification of a Ph positive CML said to be characterized by a breakpoint within the *bcr* gene, but 5′ of the cluster region itself. Following *in situ* hybridization and Northern blotting studies, the authors suggest that the *bcr* probes currently used for diagnostic purposes may miss certain Ph-positive CML cases.

Reference C9 (Benn et al., Cancer Genet Cytogenet., 29:1-7, 1987) reports that the molecular genetic analysis of *bcr* rearrangement is an important aid in the diagnosis of CML. Southern blotting with specific DNA probes is said to have potential for rapid and sensitive diagnosis, although a 5′ bcr probe is said to be required to detect some cases.

Reference C10 (Westbrook et al., PNAS, 82:8742-8746, 1985) relates to the localization and characterization of c-*abl* in the t(6;9) chromosomal translocation of acute nonlymphocytic leukemia. It is reported that, in contrast to CML, c-*abl* is not translocated from chromosome 9 and that an aberrantly sized protein is not

produced.

Referenc C11 (Trask et al., Hum. Genet., 78(3):251-259, 1988) reports that fluorescence *in situ* hybridization to interphase cell nuclei in suspension allows subsequent flow cytometric and microscopic analyses. It is said that populations of male, female, and XYY nuclei can be differentiated in this manner. Quantitative fluorescence microscopy and image processing are reported to allow the three-dimensional organization of target sequences within the nucleus to be reconstructed.

Reference C12 (Pinkel et al., PNAS, 83(9):2934-2938, 1986) relates to the use of fluorescence *in situ* hybridization for chromosome classification and for the detection of chromosomal aberrations. Biotinylated DNA probes hybridized to target chromosomes are reportedly detected following successive application of fluorescein-labeled avidin and biotinylated anti-avidin antibodies.

Reference C13 is a Dialog search report reflecting a Dialog search conducted by Applicant's attorney. The search parameters employed by Applicant's attorney are shown at the beginning of each of the various sections of the Dialog search report. Various of the articles disclosed in the present disclosure statement were identified by this particular Dialog search.

Applicant respectfully requests that the foregoing documents be made of record in the present case.

Respectfully submitted,

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Date: March 10, 1992